LUNDS UNIVERSITET

DEPARTMENT OF PSYCHOLOGY

The Effect of Depression on Pattern Separation Task Performance

Ingvill Komber & Saya Tukiainen
Bachelor thesis
2013

Supervisor: Mikael Johansson, Ph. D.,
Professor of Psychology

Abstract

The aim of this study was to investigate a possible relationship between depression and memory performance, hypothesizing a decrease in performance among participants with depression tendencies. The cognitive memory task of pattern separation was tested with four different levels of difficulty by use of a computerized memory test and the self-rating MADRS-S depression scale was used to assess the degrees of depression among the non-clinical sample of participants. Pattern separation, the cognitive ability of processing new input and distinguishing it from already stored information was tested on four levels on all participants. Participants were 40 students from Lund University, 26 women and 14 men, with a mean age of 24 (*SD* 4.19). The levels of depression were then analyzed and compared to the pattern separation task performance. The results proved the experiments ability to successfully test four levels of pattern separation demand, as every level showed an increase in difficulty. Although no significance was found between pattern separation and degree of depression, the results showed a tendency toward the hypothesized direction.

Keywords: Pattern separation, depression, neurogenesis, memory, MADRS-S, networkhypothesis

Table of Content

Although great amounts of research have been dedicated to exploring the causes, the possible treatments and the personal consequences for people suffering from depression, the knowledge accumulated is still insufficient. Previous research has indicated that several cognitive functions, including memory, might be affected by depression and this study aims to explore how and if depression among the normal population affects these subjects' performance on tasks testing memory ability.

Depression is a growing concern for public health worldwide. According to The World Health Organization (WHO), it is now the leading cause for disability in the world, affecting over 350 million people (WHO, 2012). According to other studies, approximately 13 % of the population in major European countries (Alonso, et al., 2004) and 16 % of the population in the USA (Kessler et al., 2003) are affected at least once during their lifetime. These data clarify the need to expand the current knowledge of this mood disorder and to explore possible causes so more effective treatment can be developed.

Many researchers have proposed and supported a chemical explanation to account for the causes and to develop treatments for this affective disorder, in short the chemical hypothesis. This view has come to dominate science for the past 50 years due to the development of antidepressant drugs and their shown effect. It has been presumed that affective disorders and mood variations stem from a form of chemical imbalance in the brain, which could be rectified by the use of antidepressant medication (ADs). This view is also known as the monoamine hypothesis, due to the effect of ADs on the release, reuptake and receptor sites of serotonin and norepinephrine (Bunney & Davis, 1965; Schildkraut, 1965; Nestler et al., 2002; Castrén, 2005).

In light of the widely accepted view that the brain primarily is occupied with processing and distributing information, newer research has found support for an alternative explanation for mood variations and disorders, known as the network hypothesis (Nestler et al., 2002; Castrén, 2005; Sahay, Drew & Hen, 2007). This view argues that the explanation for mood variations and various degrees of affective disorders can be found in the neuronal networks.

The two hypotheses, the chemical and the network hypotheses of mood variation, should not be seen as competitive but rather as complementary, as the release and synthesis of molecules are regulated by the activity of and affected by changes in the neuronal networks. Even though the effects of antidepressants are clearly chemical, the dependent relationship of chemical molecules on the neuronal networks pose the question whether it might be possible that the adaptive changes occurring in the concentration of

signalling molecules is a consequence of change in the information processing rather than its cause. The effect of ADs would thereby be both a directly chemical change as well as an adaptive change of the information processing of the neuronal network. It is therefore possible that ADs initiate a self-repair process, affecting both the chemical neurotransmission and the plasticity in the neuronal networks by regulating both the levels of the target signalling molecules and the firing rate of information. These effects combined can then be seen to contribute to mood elevation and change (Castrén, 2005). As the chemical variations in concentrations of molecules impact the neuronal networks by affecting both their functioning and their plasticity support for the chemical hypothesis is found. In turn, as the neuronal networks' release and processing of information can affect the concentration of the chemical molecules, the two hypotheses of mood variation, the chemical and the network hypotheses can be seen as co-existing.

An effect of ADs contribution to plasticity in the neuronal networks is increased adult neurogenesis in the mammalian hippocampal substructure called the dentate gyrus (Malberg, Eisch, Nestler & Duman , 2000) and in the olfactory bulb (Hitoshi et al., 2007). Research has found that the increase of neurogenesis correlates with the found behavioral effects produced by long-term use of antidepressants (Santarelli et al., 2003).

One other effect of AD medication that has been observed is apoptotic cell death, which coincides with an increase in neurogenesis. These results would indicate that the use of antidepressants increases a neuronal exchange, where old neurons are replaced by new, which in turn could lead to an optimization of the functionality of the neuronal connections (Sairanen, Lucas, Ernfors, Castrén & Castrén, 2005).

A mechanism that could help explain the effects antidepressants have on the plasticity of the neuronal networks in the hippocampus is brain-derived neurotrophic factor (BDNF). This neurotrophic factor is produced and released dependent on activity by neurons and has been found by research to be crucial for the selection and stabilization of active synaptic contacts (Castrén, 2005). Antidepressants as well as ECT (electroconvulsive therapy) have shown an increase of BDNF in the hippocampus and cerebral cortex (Nibuya, Morinobu & Duman, 1995; Russo-Neustadt, Beard, Huang & Cotman, 2000; Saarelainen et al., 2003) and studies have shown that injection of BDNF in transgenic mice produces the same effects normally seen after long-term use of AD medication (Siuciak et al., 1997; Shirayama, Chen, Nakagawa, Russell & Duman, 2002; Saarelainen et al., 2003; Schmidt & Duman, 2010). Transgenic mice with reduced BDNF signalling and expression do not show the same behavioral changes after the administration of antidepressants (Saarelainen et al.,, 2003),

indicating that not the mere increase of BDNF available is crucial for antidepressant effect, but rather that normal BDNF signal and expression levels are essential for this effect, as BDNF works as a mediator for neuronal activity-dependent plasticity (Castrén, 2005).

As reviewed above, neuronal plasticity, especially in the hippocampus, is intimately connected with mood elevation and change, strengthened by the network hypothesis. Research has examined several factors that possibly lead to an increase of neurogenesis in this crucial brain region; a brain area predominantly responsible for processing input, storing information to memory and retrieving already stored information (see Appendix 1). Some have explored the effects of ECT and found it to induce stronger effects than ADs, eliciting more neurogenesis in the hippocampus region of both human participants with diagnosed depression (Bolwig & Madsen) and rats (Nakamura et al., 2013).

Depression is strongly related to reduced hippocampal function on several levels, including results from several studies indicating reduced hippocampal volume (Sheline, Gado, Mokhtar & Kraemer, 1999; Bremner et al., 2000; Cole, Costafreda, McGuffin & Fu, 2011), memory deficits and a possible reduction of neurogenesis in the hippocampal substructure known as the dentate gyrus (DG) (Sahay et al., 2007).

A process found to be of much interest in this context, is the process of pattern separation, which can be described as the cognitive task of encoding new information and to differentiate between this new stimuli and already stored information, thereby permitting new stimuli, however similar to old, to be processed and stored as new information in a non-overlapping (orthogonalized) fashion (Yassa & Stark, 2011). This process involves several subregions of the hippocampus and has especially been found to stimulate activity in the dentate gyrus (Clelland et al., 2009; Aimone, Deng & Gage, 2011; Sahay, Wilson & Hen, 2011; Yassa & Stark, 2011; Nakashiba et al., 2012).

The dentate gyrus is even of particular interest when examined in the context of neurogenesis, as it produces adult born granule cells that are highly adaptive, and because neurogenesis is increased by antidepressant treatment such as ETC and antidepressant medication as mentioned earlier (Malberg et al., 2000; Duman, Malberg & Nakagawa, 2001; Bolwig & Madsen, 2007; Hitoshi et al., 2007; Sahay et al., 2007; Nakamura et al., 2012). New research on the topic has produced support for the theory that adult-born neurons in the dentate gyrus predominantly are involved with pattern separation whilst elder surviving neurons mainly focus on rapid pattern completion tasks (Nakashiba et al., 2012). When viewed in light of the effect of antidepressant treatment and medication, the

neurogenesis of the dentate gyrus and the cognitive task associated (pattern separation) could be related to mood variations and even possibly slowed by depression as earlier research has found severe effects of depression on hippocampal functioning and on neurogenesis as mentioned.

The decline in neurogenesis in the dentate gyrus caused by depression could result in reduced pattern separation task performance as previous research has explored the effect of hippocampal damage on pattern separation performance (Brock Kirwan et al., 2011) and as adult neurogenesis in the dentate gyrus is closely linked to pattern separation performance (Nakashiba et al., 2012).

Another subregion of the hippocampus also shown to be involved in pattern separation tasks is the CA3, as it processes information passed on from the dentate gyrus, which in turn is sent from the entorhinal cortex (EC). Concluding from previous research, the DG and CA3 fulfil different purposes in the pattern separation process, as the former is predominantly involved with high level pattern separation and encoding, whereas the latter is involved with lower levels of pattern separation and predominantly manages completion and retrieval, i.e. the process in which new incomplete input is put into context of already stored information and thereby becomes recognized as part of an already stored representation. The CA3 can process information passed on from the EC for pattern completion task performance. For pattern separation, however, the information is first passed from the entorhinal cortex through the dentate gyrus, before reaching CA3. As these three brain regions work conjointly, the DG, the CA3 and the EC together process incoming stimuli and are thereby able to encode incoming information and distinguish it from already stored information (Yassa & Stark, 2011).

As described above, the CA3 is involved directly with pattern separation, albeit only when the present tasks solely require low-level pattern separation, i.e. tasks involving stimuli easily distinguished from previously stored information. When the pattern separation process involves stimuli that highly resemble previously stored information, higher levels of pattern separation task performance is required. Previous research has found that when high-level pattern separation performance is required, this can only be performed successfully by the dentate gyrus (Yassa & Stark, 2011).

Pattern separation has in previous research been tested on both rodents and humans in several ways, including both healthy rodents and rodents with lesions as well as healthy humans and humans with different diagnosed deficits (Clelland et al., 2009; Aimone et al., 2011; Brock Kirwan et al., 2011; Sahay et al., 2011; Yassa & Stark, 2011;Nakashiba et al.,

2012). The most prominent test with rodents has been to compare healthy rats to rats with different hippocampal lesions when performing a spatial two-choice discrimination task. This task requires the rat to discriminate either between to locations that highly resemble one another (requiring high level pattern separation) or between to locations with lower resemblance (requiring only low level pattern separation). As expected, rats with hippocampal lesions performed significantly worse than healthy rats on the pattern separation demand task (Clelland et al., 2009).

This study aims to explore the possible effect of depression on pattern separation task performance. In light of the well-founded results from previous research, it is of great academic interest to explore if and how different levels of pattern separation relate to depression. As depression, especially when combined with stress, has shown to decrease the level of neurogenesis in the hippocampus (Hitoshi et al., 2007), it has thereby been put in relation to reduced pattern separation performance and therefore it's of great interest to explore this possible relationship further. If valid results were to be found, they could be considered a first step toward a greater understanding both of how we can measure memory but also of the impact depression has on cognitive function. Although only a first step, this study can be seen as a contribution to further the insight into how depression possibly affects memory and learning, which ultimately could contribute to better understanding of depression itself.

Pattern separation is an important cognitive function as it supports correct learning and retrieval, a vital compound of memory, which in turn enables people to correctly identify new information in their environment. If depression were to be found to impact this process, it is of interest to investigate how as this would provide insight into how people with depression view their world which in turn would be a first step toward a deeper understanding of this affective disorder.

The hypothesis for this study is that higher levels of depression should result in reduced pattern separation task performance. Will the found effects of depression on the cognitive function and neurogenesis in the hippocampus and especially on the dentate gyrus, show effect on pattern separation task performance in non-diagnosed participants? Will tasks with higher levels of pattern separation demand prove more difficult? In the following study, four different levels of pattern separation are tested and the MADRS-S rating scale for depression is used to explore possible levels of depression in non-diagnosed test subjects. The study aims to analyze a possible connection between the varying levels of pattern

separationand depression and whether a varying degree of depression has an effect on pattern separation task performance.

Method

Participants

40 individuals participated in the experiment; 26 women and 14 men, with the mean age of 24 (*SD* 4.19). The participants were students, collected from different areas and departments of Lund University. Every participant gave written consent prior to the experiment, and was at the completion of their session given cookies and cake as appreciation for their participation. All participants were fluent in Swedish and had normal or corrected to normal sight.

Design

This experiment followed a 2x4 mixed-design with two experimental factors; depression and pattern separation demand. The experiment consisted of a survey, measuring depression, and a computerized memory test, measuring pattern separation. The memory test was a spatial discrimination task thought to measure memory performance by letting participants discriminate between new and old items in a two-choice test situation. The test had four levels of pattern separation demand; high, medium high, medium low and low. Here, a high level meant more difficulty and thus, needing higher pattern separation demand. Depending on total score in the depression survey, participants were divided into two groups (no depression, depression) when analysing the results.

Material

Depression survey. A self-rating, Swedish version of Montgomery Asberg Depression Rating Scale (MADRS-S), was used to measure level of depression among participants. MADRS-S is a well known survey consisting of nine items based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for depression (Cunningham et al., 2011). Items measured are mood, feelings of unease, sleep, appetite, ability to concentrate, initiative, emotional involvement, pessimism and zest for life. Each item has seven options with scores ranging from 0 to 6, 0 being a neutral or positive approach to the item (ex.“sleeps well”) and 6 being highly negative (ex. “Sleeps extremely bad, 2-3 hours maximum”). This makes a total score range from 0 to 54. Total scores of >11 indicates a mild depression, >20 indicates likelihood for depression if the condition have lasted over a

two-week period and >40, admission to a psychiatric clinic should be considered. MADRS-S was used due to the concise and compact nature of the self-rating survey, and also the high reliability and validity in using a well known instrument. To be able to make comparisons between participants with no depression and participants with depression tendencies when analysing the results, a median split was conducted to divide participants into two groups based on their MADRS-S scores.

Memory test. The memory test material was based on a master thesis experiment conducted by Nordin (2012), which also measured pattern separation. The experiment was made using E-Prime 2.0 software and consisted of picture material that was separately created in MS Paint. All pictures had a square-system backdrop. The test items (colored squares, further described below) were then added to this constant background. The square-system consisted of 10 x 10 slightly rectangular grey squares (1,6 mm x 1,4 mm) separated by light-grey 1 millimeter thick lines, it measured in total 16,8 cm x 15 cm. Since the item-specific information was added-on within this area, the pictures kept this size at all times. Each picture was framed by a thin white frame and presented on a grey screen.

Coloring. Two sets of pictures were created as study and test items (see Figure 1, for further examples, view appendix 2). Items in both categories consisted of the grey square-system in which one or two squares, depending on which phase the item belonged to, had been colored with one of eight possible colors; green, cerise, orange, purple, turquoise, black, red and yellow. Sixteen study items, which included one colored square each, were created for every color; all colors appeared in sixteen different squares, making a total of 128 study items. For each study item, a corresponding test item was created, thus making a total of 128 study-test pairs. The test items included two squares in the same color, one being the original/old square located in the same place as in the corresponding study item, and one new colored square. The use of colors was an attempt to create individual and distinguishable items in order to be able to show a series of items in the study phase and subsequent test phase. By creating separable “characters” the need to only test memory for one item at a time was avoided.

Positioning. The new square in every test item could be positioned in one of four ways; either directly adjacent to the old square, one grey square away, two grey squares away or three grey squares away (never diagonally). These degrees of separation divided

items into the four test conditions; high (adjacent), medium high (separated by one square), medium low (separated by two squares) and low (separated by three squares). Each color was represented by four items in every separation demand condition. New squares could also be positioned in four different directions from the old square (to the right, left, above or below), these directions were evenly distributed across pattern separation levels and colors. In the end this meant that every response-key on the keyboard was meant to be used the same amount of times – the four directions was represented an equal amount of times, evenly spread across colors and levels. The outer row of squares in the system was never used; it always remained an empty frame in order not to provide participants with the possibility to "anchor" their memory of the colors onto the edges and/or corners of the picture. Thus, of the 10 x 10 square-system, only 8 x 8 squares were active.

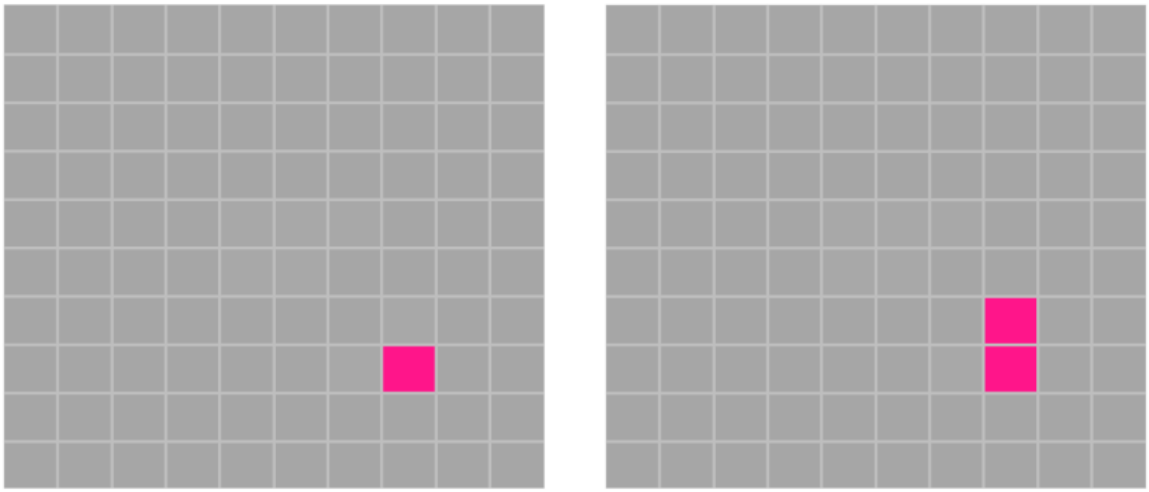


Figure 1. *Study-test pair in the high separation condition.*

Test procedure. In the study phase, four study items were displayed one after another in a sequence. Participants' only task was to memorize the location of the colored square in the square-system. In the test phase, four items paired with the ones from the study phase were displayed in a sequence – here, participants had to identify the old square by signaling its position in relation to the new square, using the arrow keys on the keyboard. These arrows signaled if the old target square was "the one to the left/right" or "the one above/below". Items were not presented in the same order in the two phases of a trial – it was not memory for a sequence that was supposed to be measured, so different orders of presentation between study and test were thought to make performance more item-specific. This procedure was repeated 32 times, with a total of 128 study-test pairs. Fixation crosses were always presented

for 500 ms in between each item. Study items were presented for 4000 ms each and test items were presented until the participant responded. Participants were instructed to provide their responses as correct and fast as possible. Every trial and its individual phases were preceded by an etiquette, signalling either that a new trial was starting or which phase would be next. The block-order was counterbalanced across participants so that the possible risk of fatigue would affect both conditions equally. The order of presentation of the sets were randomized across subjects – although individual items were not completely randomized this way, it was a practical strategy adopted in order to make sure the right study-test item-pairs always appeared together in the same trial. The fact that the block-order was counterbalanced across participants should have balanced out any potential effects of this repetition.

Material used in the memory test was inspired by the material and methods of some of the rodent studies reviewed above, that measured memory performance in relation to pattern separation demand by letting participants discriminate between old and new items presented on a computerscreen ((Talpos, McTighe, Dias, Saksida & Bussey, 2010). Although the design and materials have been modified, the basic idea has been kept intact in hopes of providing a simple and straightforward way of measuring memory performance in relation to pattern separation demand. The material was originally constructed and used in Nordin's (2012) experiment were the results, though some ceiling effects, indicated differences in performance between levels of pattern separation. The design was well based in previous research and conducted experiments, making the reliability and validity satisfying.

Procedure

To evaluate the memory test's design, pilot studies were conducted. The results from the pilot studies showed too low performance levels; hence the test was simplified and corrected before the experiment took place.

The experiment was conducted group wise in a computer room at the Department of Psychology in Lund, with maximum 4 people in each group. Every participant gave written consent prior to the experiment. Instructions about the procedure were given verbally and in written form on the computer screen at the beginning of the session.

The survey was then completed and the memory test took place. The participant was at the completion of their session given cookies and cake as appreciation for their participation. After completing the experiment, participants were asked about their performance and thoughts about the experiment and, if interested, debriefed about the aim of the study. The entire session was about 30 minutes long

Results

Presented below are results from the data collected from the memory test and MADRS-S-survey. All data was analyzed using Microsoft Office Excel and SPSS Statistics 21 software.

Survey

The measuring instrument for the MADRS-S-survey consists of categories based on participant's total score. Total scores of >11 indicates a mild depression, >20 indicates likelihood for depression if the condition have lasted over a two-week period and >40, admission to a psychiatric clinic should be considered. Participants scores on the depression survey ranged from 0 to 24, with a mean of 10.75 (*SD* 5.94). The total mean of every item measured are presented in Table 1.

Table 1. *Means of MADRS-S items.*

Item	**Mean**
Feelings of unease	2,0
Pessimism	2,0
Sleep	1,5
Ability to concentrate	1,5
Initiative	1,3
Mood	0,7
Emotional Involvement	0,7
Appetite	0,6
Zest for life	0,6

A median split was conducted to divide the participants into two groups based on degree of depression tendencies. With seven participants scoring the median score of 9, a random selection was made to split them into the two groups. The groups consisted of 20 participants in each; Group 1 with low scores (*M*= 6.25) suggesting no depression and Group 2 with higher scores *(M*= 15.25) indicating mild to moderate depression.

Memory test

Two types of data, accuracy and response times (RTs), were registered from the spatial discrimination test section of the experiment. Data from all four separation-demand levels (high, medium high, medium low, low) was analyzed in order to establish a possible connection to the degree of depression. The aim of the analyses presented in this section was

to investigate if memory performance differed in some way between the two groups (no depression, depression). Response time was measured in participants' mean response time for each pattern separation level, shown in milliseconds. Accuracy was measured by participants' mean accuracy in each pattern separation level, shown in percentage. From now on, the pattern separation levels (PS levels) are described as level 0 to 3, with 0 being the high demand and 3 being low. An initial screening for outliers in both accuracy and RT was conducted, but showed no need to exclude data. The mean RTs and accuracy for the two groups are presented in table 2, indicating minor differences between the groups. Further analyses were conducted to establish significance, described below.

Table 2. *Means for Response Times (RTs) and Accuracy in the Memory Test in Separation Demand Condidions, over the two groups.*

RT (ms)

Pattern separation level	No depression	Depression tendencies
PS level 0	2245	1991
PS level 1	1921	1865
PS level 2	1771	1751
PS level 3	1742	1855

Accuracy

Pattern separation level	No depression	Depression tendencies
PS level 0	.62	.59
PS level 1	.71	.62
PS level 2	.65	.72
PS level 3	.70	.66

Accuracy. A one-way repeated measures ANOVA was conducted to compare total accuracy at the four levels of pattern separation demand. The result indicated a substantial significant effect in accuracy, Wilks' Lambda = .61, $F(3,37)=7.94$, $p <.0005$, multivariate partial eta squared = .39. A pair wise comparison with Bonferroni corrections indicated that the mean accuracy score for PS level 0 (*M = .606, SD = .088)* was significantly lower than the mean score for PS level 2 *(M = .686, SD = .118)* and PS level 3 *(M = .681, SD*

= .082). The mean accuracy score for PS level 1 *(M = .666, SD = .115)* did not differ significantly from any of the other PS levels.

A mixed between-within subjects analysis of variance was conducted to assess the impact of the two depression-groups on participants' accuracy on the memory test's four levels of pattern separation demand. No interaction effect between group belonging and accuracy was found, Wilks' Lambda = .96, $F(3,36)= .51$, $p = .677$, partial eta squared = .041. The analysis revealed a main effect on pattern separation demand, Wilks' Lambda = .61, $F(3,36)= 7.736$, $p < .0005$, partial eta squared = .392., indicating a substantial increase in accuracy across the four levels, 0 to 3. The main effect comparing the two groups of depression was not significant $F(1,38)= 1.528$, $p = .224$, partial eta squared = .039, suggesting no difference in accuracy between the groups.

Response times. A one-way repeated measures ANOVA was conducted to compare response times (RT) at the four levels of pattern separation demand. The results showed significant effect in response time, Wilks' Lambda = .66 F(3, 37)=6.35, p = .001, multivariate partial eta squared = .34. A pair wise comparison with Bonferroni corrections indicated that the mean response time, measured in milliseconds, for PS level 0 (M = 2119, SD = 771) was significantly higher than the mean response times for all the other PS levels; PS level 1 (M = 1893, SD = 627), PS level 2 (M = 1761, SD = 537) and PS level 3 (M = 1798, SD = 656). No significant differences were found among any of the other PS levels.

Another mixed between-within subjects analysis of variance was conducted to explore the impact of the two different depression-groups on participants' response times (RTs) on the memory test's four levels of pattern separation demand. No interaction effect between group belonging and RT was found, Wilks' Lambda = .91, $F(3,36)= 1.263$, $p = .302$, partial eta squared = .095. A main effect on pattern separation was found, Wilks' Lambda = .65, $F(3,36)= 6.389$, $p = .001$, partial eta squared = .347, showing a decrease in RT across the four levels, 0 to 3. The main effect comparing the two groups was not significant, Wilks' Lambda $F(1,38)= .082$, $p = .776$, partial eta squared = .002, suggesting no difference in response time between the groups.

Correlation

Pearson product-moment correlation coefficient was used to discover possible correlations among PS levels and MADRS-S scores, using the MADRS-S scores as a continuous variable without groupings. Preliminary analyses were performed to ensure no

violation of the assumptions of normality, linearity and homoscedasticity. The results are presented in Table 3. A medium, negative correlation was found between MADRS-S score and Total Accuracy PS level 3, $r = -.32$, $n = 40$, $p < .05$. Two medium, negative correlations was also found between Total Accuracy PS level 2 and Total Response Time PS level 2, $r = -.35$, $n = 40$, $p < .05$, and Total Response Time PS level 3, $r = -.34$, $n = 40$, $p < .05$. All PS levels in Response Time correlated highly positive with each other.

Table 3. *A Pearson product-moment correlation coefficient of participants MADRS-S scores and all Pattern Separation Levels of Accuracy and Response Time.*

Scale	**1.**	**2.**	**3.**	**4.**	**5.**	**6.**	**7.**	**8.**	**9.**
1. Total MADRS-S	-	-.122	.270	-.036	-.315*	-.122	-.038	-.066	-.005
2. Total Accuracy PS level 0		-	.091	.009	.308	-.006	-.123	-.251	-.212
3. Total Accuracy PS level 1			-	.152	.076	.183	.039	-.068	-.096
4. Total Accuracy PS level 2				-	.027	-.022	-.177	-.351*	-.337*
5. Total Accuracy PS level 3					-	.029	-.011	-.110	-.096
6. Total Response Time PS level 0						-	.851**	.732**	.628**
7. Total Response Time PS level 1							-	.846**	.815**
8. Total Response Time PS level 2								-	.888**
9. Total Response Time PS level 3									-

* $p < .05$ (2-tailed).
** $p < .01$ (2-tailed).

In sum, no interaction between pattern separation level and depression was found. A main effect for pattern separation demand was present in both accuracy and response time, with PS level 0 being the toughest and PS level 3 the easiest. Participants' scores on the survey ranged from 0 to 24, with a mean of 10.75 (*SD* 5.94).

Discussion

Participants performances on the memory test were sufficient, the mean accuracy was at its lowest on a mean level of 60 %. The means of the PS levels indicates, as predicted, an increase of accuracy and a decrease of RT over the four levels, 0 to 3, which with further analyzing proved to be significant. Thus, the design successfully reflected the four levels of separation demand with the highest demand being the hardest to process and the lowest being the easiest. Overall, the result in accuracy and RT corresponds with the original design results, conducted by Nordin (2012). Since a modification in PS levels had been done, a decrease in ceiling effect was achieved.

When analyzing the results, no interaction effect was found between depression and pattern separation in either accuracy or RT, neither was a main effect comparing the two groups results. Hypothesizing a difference between the groups, the null hypothesis can therefore not be rejected.

However, although the results show no significant difference in performance between the two groups, they show tendency toward the hypothesized direction (*see table 2.)*. The results in the memory test are interesting and indicate different patterns between the groups, whereas group 1 (no depression) are closer to the expected results with PS level 0 being the most difficult and PS level 3 the least, group 2 (depression tendencies) shows a different pattern which we will discuss further below. Comparing the groups mean accuracy across pattern separation levels, it becomes evident that group 2 performed worse in all but one of the separation levels, level 2. This is an interesting result as group 2 is the group with depression tendencies, thus the results are in line with our hypothesis. Additional research is needed to explore this effect further. It is possible that a stronger effect might be found in patient groups with diagnosed MDD (Major Depressive Disorder) or possibly another affective or anxiety disorder. Given the body of research supporting the hypothesis that depression affects hippocampal function, it is likely that this effect will be found when testing pattern separation in future research. It is however possible that an actual disorder, hippocampal lesion or damage is needed to detect a significant covariation with pattern separation.

Looking at the response time, group 2 answered faster in all levels except for the easiest one, level 3. Group 2 performed best in pattern separation level 2, which has the fastest response time and by far the highest accuracy. Group 1 performed best in pattern separation level 3, as expected. This is a noteworthy result in light of the groups' makeup. As group 2 has higher depression levels than group 1, their scores on MADRS-S might be a contributing factor to this result, which could indicate a bias toward attending less intently on easier tasks.

Ranging from 0 to 24 with a mean of 10.75 (SD = 5.94), the MADRS-S scores collected seem fairly high as scores above 11 indicate a mild depression. It's no news that students suffer from stress and poor sleep; pessimism, feelings of unease and sleep were the items with the highest scores, making students a population of interest in this matter. However, as mentioned earlier, in order to detect a possible significant relationship between depression and pattern separation, further research with a population diagnosed with depression is essential. Perhaps another instrument for measuring depression is required, but more importantly, collecting a wider range of scores would be preferable.

An additional error in detecting significance might be the similarity of the two groups. The median split that was conducted was somewhat in line with the measurement categories, but with the median being 9 and the limit for mild depression being 11, Group 2 consists of some participants slightly under the limit for mild depression. In defence, a score of 9 shows tendency towards mild depression and the goal of using the survey is not to diagnose but to discover possible differences in performance in the memory test due to depression tendencies. Another difficulty is the high trend in scoring 9 on the survey, which could possibly make the groups to equal and thus impair the chance of significant results. This being taken under consideration, additional analyses of all data was conducted without data from all but one of the participants with a score of 9. Although those analyses intensified the previously found results, the differences were minor and insignificant. Hence, the data from all participants was used to enhance the power. However, in the correlation studies described above, MADRS-S scores were used as a continuous variable without groupings to access the full, cohesive effect. Group correlations were not the main interest since the low number of participants and, possibly, the small variety between the groups. If a bigger sample would be collected, participant groups could be divided in line with the measuring instrument categories. This would also with greater likelihood include participants with scores above 40, indicating a need for hospitalization, which in turn possibly could yield more significant results and enhance the power and the effect size of the study.

The correlation analyses also indicate noteworthy results. The MADRS-S scores only negatively correlate with Accuracy PS level 3, which possibly indicates a tendency for participants with higher depression levels to view the task as more complicated than necessary and thus performing less well on it than on the more difficult levels. Viewing this in light of the response time results discussed earlier, a higher depression score might lead to a bias for more difficult tasks. In order to gain further insight into this effect, other types of tests and studies need to be conducted.

All response times correlate highly positively with one another, suggesting a tendency among participants to respond in the same, individual, pace in all levels. This suggests that participants have a certain pace during every level throughout the entire test. Participants who answer fast during one level are more likely to respond fast during another level, which keeps in line with the knowledge that people work and process information at different paces.

Accuracy in level 2 negatively correlates with response time in both level 2 and 3. This result could indicate a tendency for participants to overlook the difference in difficulty between level 2 and 3, possibly viewing the two levels as the same. Strengthening this

assumption is the fact that the faster participants responded in level 2 and 3, the less accurate their responses were in level 2. In light of the increased difficulty in level 2, participants tending toward faster responses might overlook this and therefore not devoting the amount of attention needed for increased accuracy for the higher level PS demand.

The field of depression and it's impact on pattern separation is still, to this day, not fully researched and in need of further exploration. As mentioned earlier, depression is now afflicting over 350 million people worldwide and is the main reason for disability, making it a global public health issue. In this study, no diagnosed subjects were included, although the ratings on the MADRS-S scale indicate a clear variation of depression levels among participants. This result alone proves the prevalence of depression and stresses the need for further study as it strengthens the results from previous research which proposed that as many as 13 % of all Europeans are afflicted by depression at some point in their lives (ESEMeD, 2004).

The results from this study show no significant indication that the reported depression levels led to a reduced pattern separation task performance. However, the results between the two groups differ from one another, indicating a tendency that depression levels might influence pattern separation task performance as discussed earlier.

As reviewed in this paper, the hippocampus can be strongly affected by depression, some studies indicating a reduced hippocampal volume as an effect of the mood disorder. However it is still unknown whether the reduced hippocampal volume is caused by depression or whether depression in some cases might be an effect of reduced hippocampal volume. Research on the area indicate several possible precursors for this volume reduction including results indicating that maltreatment during childhood might lead to this effect in later life (Teicher, Anderson & Polcari, 2011).

Antidepressant medication has a long history of success as a treatment of depression. It has one drawback however. AD medication has not produced an improvement in all patients receiving them. Research on the relatively recent developed positive psychology influenced psychotherapy indicates that patients might respond better and have higher nimprovement rates when receiving this type of psychotherapy than the otherwise highly recommended combination of AD medication and conventional psychotherapy (Seligman, Rashid & Parks, 2006). These results give reinforcement to the need for further exploration of the possible treatment and origin of depression as it sheds new light on the effects of AD medication and their limitations. However, further research connecting this new

psychotherapy to neurogenesis is necessary to strengthen the connection to the neuropsychological findings relating neurogenesis to depression.

That the effects of AD medication are not identical in all receivers is known within the scientific community. The reasons behind this fact are however, still unknown. As these results indicate, additional research is also needed to deepen the knowledge on the exact effects of different antidepressants and on how different types or levels of depression might make people respond to the same medication differently. Since AD medication has been shown to reverse the negative effects depression has on hippocampal function, furthering this knowledge is also important in relation to pattern separation, as the patients for whom AD medication does not have the desired effect, possibly are in need of some other treatment to produce it. To this day the most successful treatment of depression, to also produce an increase in neurogenesis, is ECT and relating this treatment to pattern separation has yet to be accomplished.

It is possible, in view of the network hypothesis, that exercising pattern separation could result in an increase of neurogenesis and even possibly have an antidepressant effect, which in turn could lend support to the shown effect of psychotherapy. If this effect could be proven to exist, it also might lend support for the found results in our study as depression scores had low to no effect on pattern separation performance.

The results of this study could also be an effect of the used sample. As participants were students, the reliability could be questioned, as university students could be considered a homogenic group, thus not representative for the world population as such. However, as students have diverse backgrounds and generally belong to the normal population, the results could be seen as an indication of relationships between the variables, if not a confirmation.

In this study, depression is viewed as an affective mood disorder, consistent with the view of clinical psychology and in line with results from previous research. However, if this view were to be changed and depression were to be seen as an alternate state of mind, essential for creativity, it might also be possible that the changes occurring in the brain as an effect of depression might not be malignant but rather an adaptive change due to creativity. This effect is debated however, as research is inconclusive regarding depressions relation to creativity, with some studies indicating a strong relationship (Kyaga et al., 2013) and others only finding indications of a relationship if at all (Silvia & Kimbrel, 2010).

In conclusion, being an interesting and arising field of research, the future holds many opportunities and reasons for additional explorations of depression, both as its own field of study and in combination with memory research. The understanding of the impact of

depression on both pattern separation and other types of memory functions is vital to develop successful treatment in the future.

References

Aimone, J. B., Deng, W. & Gage, F.H. (2011) Resolving new memories: A critical look at the dentate gyrus, adult neurogenesis, and pattern separation. *Neuron, 70.* doi: 10.1016/j.neuron.2011.05.010

Alonso, J., Angermeyer, M. C., Bernert, S., Bruffaerts, R., Brugha, T. S., Bryson, H. et al. (2004) Prevalence of mental disorders in Europe: Results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project, *Acta Psychiatrica Scandinavica* Vol 109(Suppl420), 21-27.

Bunney, W. E., Davis, J. M., (1965) Norepinephrine in Depressive Reactions A Review, *Arch Gen Psychiatry,*13 (6), 483-494

Bolwig, T. G., Madsen, T. M. (2007**)** Electroconvulsive therapy in melancholia**:** the role of hippocampal neurogenesis, *Acta Psychiatrica Scandinavica. Supplementum* (433), 130-5

Bremner, J., Vythilingam, D., Vermetten, M., Nazeer, E., Adil, A., Khan, J. et al. (2002) Reduced volume of orbitofrontal cortex in major depression, *Biological Psychiatry*, Vol 51(4), 273-279

Brock Kirwan, C., Hartshorn, A., Stark, S.M., Goodrich-Hunsaker, N.J., Hopkins, R.O. & Stark, C.E.L. (2012) Pattern separation deficits following damage to the hippocampus, *Neuropsychologia, 50,* 2408-2414

Castrén, Eero (2005) Is mood chemistry? *Nature Reviews Neuroscience, vol 6, 241-246*

Clelland, C. D., Choi, M., Romberg, C., Clemenson Jr., G. D., Fragniere, A., Tyers, P. et al. (2009) A functional role for adult hippocampal neurogenesis in spatial pattern separation, *Science* (Vol. 325 (5937), 210-3

Cole, J., Costafreda, S. G., McGuffin, P. & Fu, C. H (2011)
Hippocampal atrophy in first episode depression: a meta-analysis of magnetic resonance imaging studies, *Journal Of Affective Disorders* Vol. 134 (1-3), 483-7

Duman, R. S., Malberg, J. & Nakagawa, S. (2001)
Regulation of adult neurogenesis by psychotropic drugs and stress, *The Journal Of Pharmacology And Experimental Therapeutics* Vol. 299 (2), 401-7

Hitoshi, S., Maruta, N., Higashi, M., Kumar, A., Kato, N. & Ikenaka, K. (2007)
Antidepressant drugs reverse the loss of adult neural stem cells following chroni c stress, *Journal Of Neuroscience Research* Vol. 85 (16), 3574-85

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K. R., Rush, A. J., Walters, E. E. & Wang, P. S. (2003) The Epidemiology of Major Depressive Disorder: Results From the National Comorbidity Survey Replication (NCS-R) *JAMA* Vol. 289 (23)

Kyaga, S., Landén, M., Boman, M., Hultman, C., Långström & Lichtenstein P. (2013) Mental illness, suicide and creativity, *Journal of Psychiatric Research* Vol. 47 (1), 83-90

Malberg, J. E., Eisch, A. J., Nestler, E. J. & Duman, R. S. (2000)
Chronic antidepressant treatment increases neurogenesis in adult rat hippocamp us, *The Journal Of Neuroscience: The Official Journal Of The Society For Neuroscience* Vol. 20 (24), 9104-10

Nakamura, K., Ito, M., Liu, Y., Seki, T., Suzuki, T. & Arai, H. (2013)
Effects of single and repeated electroconvulsive stimulation on hippocampal cell proliferationand spontaneous behaviors in the rat, *Brain Research* Vol. 1491, 88-97

Nakashiba, T., Cushman, J. D., Pelkey, K. A., Renaudineau, S., Buhl, D. L., McHugh, T. J. et al. (2012) Young dentate granule cells mediate pattern separation, whereas old granule cells facilitate pattern completion *Cell* Vol. 149 (1), 188-201

Nestler, E. J., Barrot, M., DiLeone, R. J., Eisch, A. J., Gold, S. J. & Monteggia, L. M. (2002) Neurobiology of depression, *Neuron* Vol. 34 (1), 13-25

Nibuya, M., Morinobu, S. & Duman, R. S. (1995) Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive s eizure and antidepressantdrug treatments, *The Journal Of Neuroscience: The Official Journal Of The Society For Neuroscience* Vol. 15 (11), 7539-47

Nordin, K. (2012) *Spatial discrimination performance at levels of pattern separation demand after global/local processing*, Master thesis, Lund University, Department of Psychology.

Russo-Neustadt, A. A., Beard, R. C., Huang, Y. M. & Cotman, C. W. (2000) Physical activity and antidepressant treatment potentiate the expression of specif ic brain-derivedneurotrophic factor transcripts in the rat hippocampus, *Neuroscience* Vol. 101 (2), 305-12

Saarelainen, T., Hendolin, P., Lucas, G., Koponen, E., Sairanen, M., MacDonald, E. et al. (2003) Activation of the TrkB neurotrophin receptor is induced by antidepressant drugs and is require d for antidepressant-induced behavioral effects, *The Journal Of Neuroscience: The Official Journal Of The Society For Neuroscience* Vol. 23 (1), 349-57

Sahay, A., Drew, M. R. & Hen, R. (2007) Adult hippocampal neurogenesis in depression, *Nature Neuroscience,* Vol. 10 (9), 1110-15

Sahay, A., Drew, M. R. & Hen, R. (2007) Dentate gyrus neurogenesis and depression, *Progress In Brain Research*, Vol. 163, 697-722

Sahay, A., Wilson, D. A. & Hen, R. (2011) Pattern separation: A common function for new neurons in hippocampus and olfactory bulb, *Neuron* vol. 70, 582-588

Santarelli, L., Saxe, M., Gross, C., Surget, A., Battaglia, F., Dulawa, S. et al. (2003) Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants, *Science* Vol. 301 (5634), 805-9

Sairanen, M., Lucas, G., Ernfors, P., Castrén, M. & Castrén, E. (2005) Brain-derived neurotrophic factor and antidepressant drugs have different but coordina ted effects onneuronal turnover, proliferation, and survival in the adult dentate gyrus, *The Journal Of Neuroscience: The Official Journal Of The Society For Neuroscience* Vol. 25 (5), 1089-94

Schildkraut, J. J. (1965) The catecholamine hypothesis of affective disorders: a review of supporting evidence, *The Journal Of Neuropsychiatry And Clinical Neurosciences* Vol. 7 (4), 524-33

Schmidt, H. D. & Duman, R. S. (2010) Peripheral BDNF produces antidepressant-like effects in cellular and behavioral models, *Neuropsychopharmacology: Official Publication Of The American College Of Neuropsychopharmacology* Vol. 35 (12), 2378-91

Seligman, M. E. P., Rashid, T., Parks, A. C. (2006) Positive psychotherapy, *American Psychologist,* vol. 61, 8.

Sheline, Y., Gado, I., Mokhtar, H. & Kraemer, H. C. (2003) Untreated depression and hippocampal volume loss, *The American Journal of Psychiatry* Vol 160(8), 1516-1518

Shirayama,Y., Chen, A. C., Nakagawa, S., Russell, D. S & Duman, R. S. (2002) Brain-derived neurotrophic factor produces antidepressant effects in behavioral models of depression, *The Journal Of Neuroscience: The Official Journal Of The Society For* Vol. 22 (8), 3251-61

Silvia, P. J. & Kimbrel, N. A. (2010) A Dimensional Analysis of Creativity and Mental Illness: Do Anxiety and Depression Symptoms Predict Creative Cognition, Creative Accomplishments, and Creative Self-Concepts? *Psychology of Aesthetics, Creativity, and the Arts* Vol. 4 (1), 2-10

Siuciak, Judith A. (1997) Antidepresseant-like effect of brain-derived neurotrophic factor, *Pharmacology Biochemistry and Behavior* Vol 56 (1), 131-137

Talpos, J. C., McTighe, S. M., Dias, R., Saksida, L. M. & Bussey, T. J. (2010) Trial-unique, delayed nonmatching-to-location (TUNL): a novel, highly hippocampus-dependent automated touchscreen test of location memory and pattern separation, *Neurobiology of learning and memory,* Vol. *9*4 (3), 341-52

Teicher, M. H., Anderson, C. M. & Polcari, A. (2012) Childhood maltreatment is associated with reduced volume in the hippocampal s ubfields CA3, dentate gyrus, and subiculum, *Proceedings Of The National Academy Of Sciences Of The United States Of America,* Vol. 109 (9), 563-72

World Health Organization (WHO) (2012). Depression. Fact Sheet 369. Retrieved January 7 2013 from WHO: http://www.who.int/mediacentre/factsheets/fs369/en/

Yassa, M.A. & Stark, C.E.L., (2011) Pattern separation in the hippocampus, *Trends in Neuroscience* Vol. 34 (10), 515-25

Appendix 1. Glossary

Adult neurogenesis: The process in which new neurons are generated in neural stem cells during adulthood. It is known to occur in two pathways; the subventricular zone (eliciting neurons in the olfactory bulb) and the subgranular zone (generating new granule cells in the dentate gyrus).

CA3: Subregion of the hippocampus, it is one of the four main histological divisions. It receives information from the EC directly (inducing pattern completion) and from the EC through the dentate gyrus (inducing pattern separation).

Dentate gyrus (DG): Subregion of the hippocampus, most prominently involved with pattern separation, it consist of small neurons called granule cells, which have been shown to be generated through adulthood, making the DG prominent in research of adult neurogenesis.

Entorhinal cortex (EC): Brain region located in the parahippocampal gyrus. Due to its anatomical connections to parts of the hippocampus, it is considered part of the hippocampal region. It also has several connections to the Cerebral Cortex among several other brain regions. It can therefore be seen as a region processing complex information deriving from multiple brain areas and regions.

Granule cells: Small neurons found throughout the brain that have diverse properties, both functionally and anatomically. In the DG, granule cells have axons that project to the CA3 cells and interneurons.

Hippocampus: A major brain component in humans, belonging to the limbic system, which is most prominently involved with learning and storing information. It plays a vital role in processing information from short-term memory to long-term memory and in spatial navigation. It is intimately connected to the cerebral cortex and is located underneath the cortical surface in the medial temporal lobe. It consists of several subregions, including the DG and the CA3.

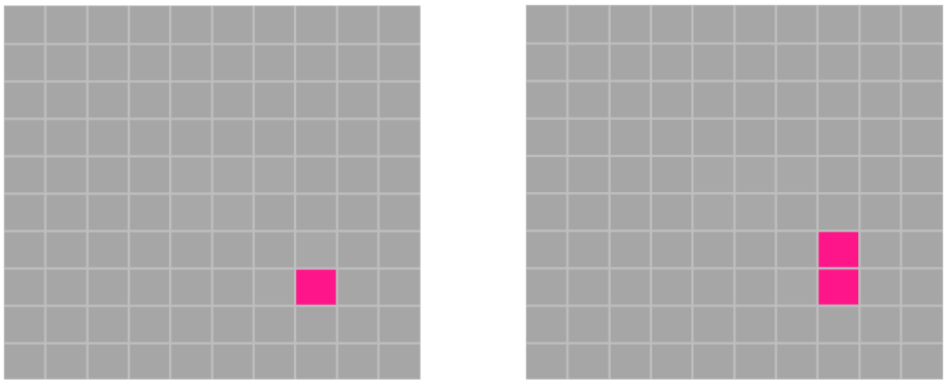
Olfactory Bulb: Brain structure located in the forebrain. It processes olfactory information, detected by cells in the nasal cavity. It is one area shown to produce adult neurogenesis, suggested to be involved with olfactory pattern separation processes.

Pattern Completion: In short, the process in which new input is seen to fit into already stored patterns of information, which in turn are used to process this information. This new input is then stored as part of previously stored information.

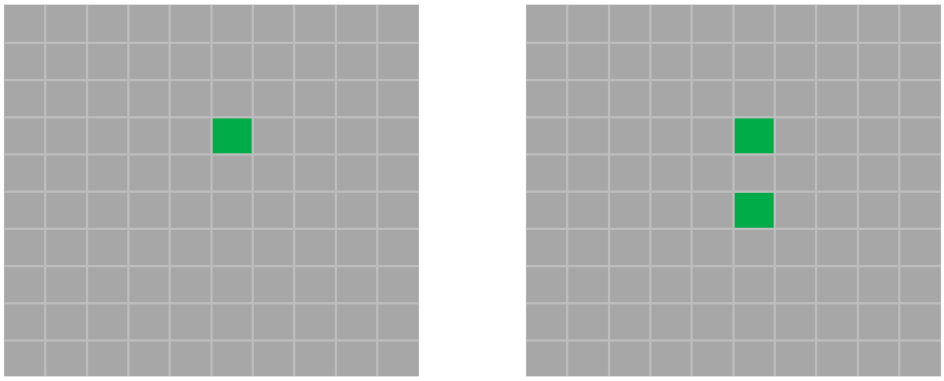
Pattern Separation: In short, the direct opposite to pattern completion, it is the process in which new information is seen as separate and not overlapping with previously stored information, however similar it might be. This process thus enables new input to be stored as new separate units.

Appendix 2. Examples of images from the memory test material in all pattern separation levels.

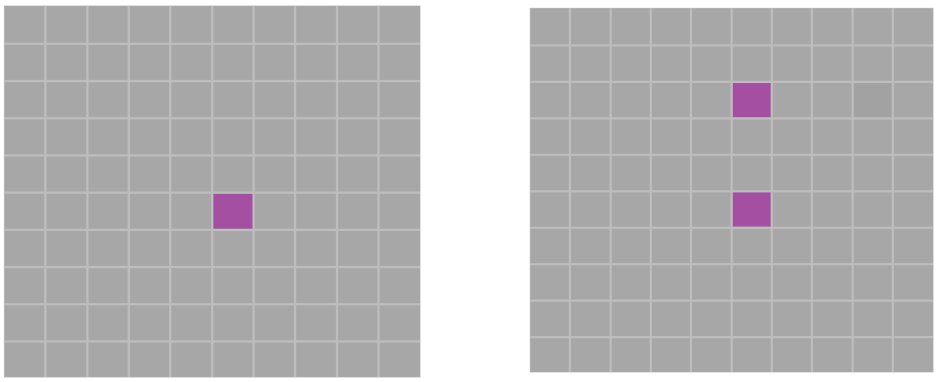
a.

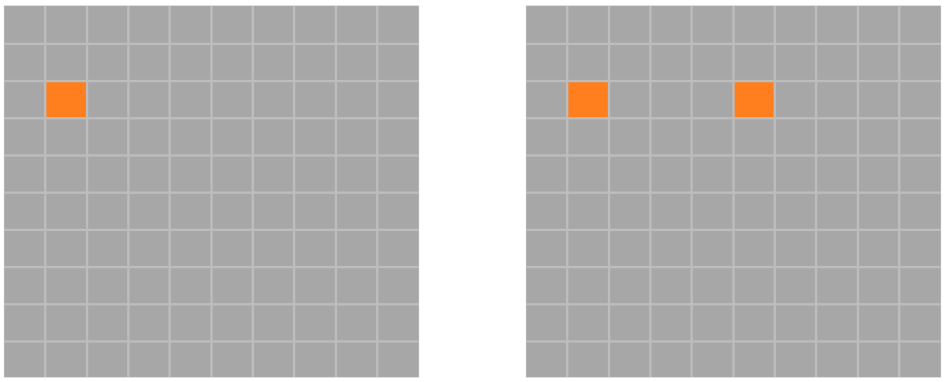


b.



c.



d. 

a. Study-Test pair in high pattern separation demand, PSlevel0. **b**. Study-Test pair in medium high pattern separation demand, PSlevel1. **c**. Study-Test pair in medium low pattern separation demand, PSlevel2. **d**. Study-Test pair in low pattern separation demand, PSlevel3.